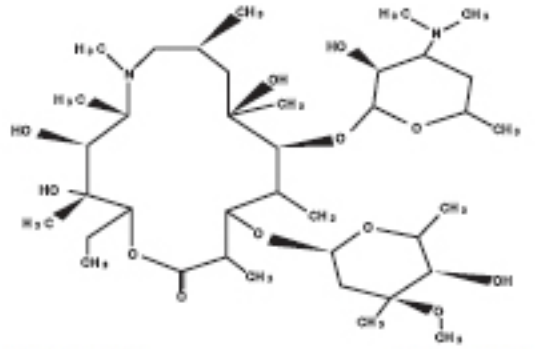
AZITHROMYCIN - azithromycin monohydrate injection, powder, lyophilized, for solution
APP Pharmaceuticals, LLC

*For **IV** infusion only*
Rx only
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Azithromycin for Injection and other bacterial drugs, Azithromycin for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

Azithromycin for Injection contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for intravenous injection. Azithromycin has the chemical name *(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L*-*ribo*hexopyranosyl) oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D*-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Azithromycin has the following structural formula:



Azithromycin, as the monohydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}•H_2O$ and a molecular weight of 766.5.
Azithromycin for Injection consists of azithromycin monohydrate and the following inactive ingredients: citric acid and sodium hydroxide. Azithromycin for Injection is supplied in lyophilized form in a 10 mL vial equivalent to 500 mg of azithromycin for intravenous administration. Reconstitution, according to label directions, results in approximately 5 mL of azithromycin for intravenous injection with each mL containing azithromycin monohydrate equivalent to 100 mg of azithromycin. After reconstitution each mL contains: azithromycin monohydrate equivalent to 100 mg of azithromycin, 76.9 mg of citric acid, and sodium hydroxide for pH adjustment.

CLINICAL PHARMACOLOGY

In patients hospitalized with community-acquired pneumonia receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/mL, the mean C_{max} ± S.D. achieved was 3.63 ± 1.60 mcg/mL, while the 24-hour trough level was 0.20 ± 0.15 mcg/mL, and the AUC_{24} was 9.60 ± 4.80 mcg•h/mL.
The mean C_{max}, 24-hour trough and AUC_{24} values were 1.14 ± 0.14 mcg/mL, 0.18 ± 0.02 mcg/mL, and 8.03 ± 0.86 mcg•h/mL, respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/mL. Similar pharmacokinetic values were obtained in patients hospitalized with community-acquired pneumonia that received the same 3-hour dosage regimen for 2 to 5 days.
Plasma concentrations (mcg/mL ± S.D.)
after the last daily intravenous infusion
of 500 mg azithromycin

Infusion Concentration, Duration	Time after starting the infusion (hr)			
2 mg/mL, 1 hr[a]	0.5 2.98 ± 1.12	1 3.63 ±1.73	2 0.60 ± 0.31	3 0.40 ± 0.23
1 mg/mL, 3 hr[b]	0.91 ± 0.13	1.02 ± 0.11	1.14 ± 0.13	1.13 ± 0.16

**Plasma concentrations (mcg/mL ± S.D.)
after the last daily intravenous infusion
of 500 mg azithromycin (continued)**

Infusion Concentration, Duration	Time after starting the infusion (hr)				
2 mg/mL, 1 hr[a]	4 0.33 ± 0.16	6 0.26 ± 0.14	8 0.27 ±0.15	12 0.20 ±0.12	24 0.20 ±.15
1 mg/mL, 3 hr[b]	0.32 ± 0.05	0.28 ±0.04	0.27 ±0.03	0.22 ±0.02	0.18 ±0.02

[a] = 500 mg (2 mg/mL) for 2 to 5 days in Community-acquired pneumonia patients.

[b] = 500 mg (1 mg/mL) for 5 days in healthy subjects.

The average CL_t and V_d values were 10.18 mL/min/kg and 33.3 L/kg, respectively, in 18 normal volunteers receiving 1000 to 4000 mg doses given as 1 mg/mL over 2 hours.

Comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500 mg intravenous azithromycin showed only an 8% increase in C_{max} but a 61% increase in AUC_{24} reflecting a threefold rise in C_{24} trough levels.

Following single oral doses of 500 mg azithromycin to 12 healthy volunteers, C_{max}, trough level, and AUC_{24} were reported to be 0.41 mcg/mL, 0.05 mcg/mL, and 2.6 mcg•h/mL, respectively. These oral values are approximately 38%, 83%, and 52% of the values observed following a single 500 mg I.V. 3-hour infusion (C_{max}: 1.08 mcg/mL, trough: 0.06 mcg/mL, and AUC_{24}: 5 mcg•h/mL). Thus, plasma concentrations are higher following the intravenous regimen throughout the 24-hour interval. The pharmacokinetic parameters on day 5 of azithromycin 250 mg capsules following a 500 mg oral loading dose to healthy young adults (age 18 to 40 years old) were as follows: C_{max}: 0.24 mcg/mL, AUC_{24}: 2.1 mcg•h/mL. Tissue levels have not been obtained following intravenous infusions of azithromycin. Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios following oral administration of azithromycin are shown in the following table:

AZITHROMYCIN CONCENTRATIONS FOLLOWING
TWO - 250 mg (500 mg) CAPSULES IN ADULTS

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION (mcg/g or mcg/mL)[1]
SKIN	72 to 96	0.4
LUNG	72 to 96	4
SPUTUM*	2 to 4	1
SPUTUM**	10 to 12	2.9
TONSIL***	9 to 18	4.5
TONSIL***	180	0.9
CERVIX****	19	2.8

AZITHROMYCIN CONCENTRATIONS FOLLOWING
TWO - 250 mg (500 mg) CAPSULES IN ADULTS
(continued)

TISSUE OR FLUID	CORRESPONDING PLASMA OR SERUM LEVEL (mcg/mL)	TISSUE (FLUID) PLASMA (SERUM) RATIO[1]
SKIN	0.012	35
LUNG	0.012	>100
SPUTUM*	0.64	2
SPUTUM**	0.1	30
TONSIL***	0.03	>100
TONSIL***	0.006	>100
CERVIX****	0.04	70

[1]High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of azithromycin is pH related. Azithromycin is concentrated in cell lysosomes which have a low intraorganelle pH, at which the drug's activity is reduced. However, the extensive distribution of drug to tissues may be relevant to clinical activity.
* Sample was obtained 2 to 4 hours after the first dose.
** Sample was obtained 10 to 12 hours after the first dose.
*** Dosing regimen of 2 doses of 250 mg each, separated by 12 hours.
****Sample was obtained 19 hours after a single 500 mg dose.
Tissue levels were determined following a single oral dose of 500 mg azithromycin in 7 gynecological patients. Approximately 17 hours after dosing, azithromycin concentrations were 2.7 mcg/g in ovarian tissue, 3.5 mcg/g in uterine tissue, and 3.3 mcg/g in salpinx. Tissue levels have not been obtained following intravenous infusion of azithromycin.
In a multiple-dose study in 12 normal volunteers utilizing a 500 mg (1 mg/mL) one-hour intravenous-dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11% after the 1st dose and 14% after the 5th dose. These values are greater than the reported 6% excreted unchanged in urine after oral administration of azithromycin. Biliary excretion is a major route of elimination for unchanged drug, following oral administration.
The serum protein binding of azithromycin is variable in the concentration range approximating human exposure decreasing from 51% to 0.02 mcg/mL to 7% at 2 mcg/mL.

Microbiology
Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.
Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after one hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.
Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in **INDICATIONS AND USAGE.**
Aerobic gram-positive microorganisms
Staphylococcus aureus
Streptococcus pneumoniae
NOTE: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to azithromycin.
Aerobic gram-negative microorganisms
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
"Other" microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Legionella pneumophila

Mycoplasma hominis
Mycoplasma pneumoniae
Beta-lactamase production should have no effect on azithromycin activity.
Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for azithromycin tablets and azithromycin for oral suspension.
Aerobic gram-positive microorganisms
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Aerobic gram-negative microorganisms
Haemophilus ducreyi
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
"Other" microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae
The following*in vitro* data are available, **but their clinical significance is unknown.**
Azithromycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 0.5 mcg/mL or less against most (≥ 90%) strains of streptococci listed below and MIC's of 2 mcg/mL or less against most (≥ 90%) strains of other listed microorganisms. However, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.
Aerobic gram-positive microorganisms
Streptococci (Groups C, F, G)
Viridans group streptococci
Aerobic gram-negative microorganisms
Bordetella pertussis
Anaerobic microorganisms
Peptostreptococcus species
Prevotella bivia
"Other" microorganisms
Ureaplasma urealyticum

Susceptibility Tests
Azithromycin can be solubilized for *in vitro* susceptibility testing using dilution techniques by dissolving in a minimum amount of 95% ethanol and diluting to the working stock concentration with broth.

Dilution Techniques
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.
Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of azithromycin powder. The MIC values should be interpreted according to the following criteria:
For testing aerobic microorganisms other than *Haemophilus* species, *Neisseria gonorrhoeae*, and streptococci:

MIC (mcg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

For testing *Haemophilus* species:[a]

MIC (mcg/mL)	Interpretation

≤ 4	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility testing with *Haemophilus* species using *Haemophilus* Test Medium (HTM)[1]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing streptococci including *S. pneumoniae:*[b]

MIC (mcg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1	Intermediate (I)
≥ 2	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1]

No interpretive criteria have been established for testing *Neisseria gonorrhoeae.* This species is not usually tested.

A report of "Susceptible" indicates that the pathogen is likely to respond to monotherapy with azithromycin. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that achievable drug concentrations are unlikely to be inhibitory; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard azithromycin powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
Haemophilus influenzae ATCC 49247[a]	1 to 4
Staphylococcus aureus ATCC 29213	0.5 to 2
Streptococcus pneumoniae ATCC 49619[b]	0.06 to 0.25

[a] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)[1].

[b] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1]

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 mcg azithromycin to test the susceptibility of microorganisms to azithromycin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15-mcg azithromycin disk should be interpreted according to the following criteria:

For testing aerobic microorganisms (including streptococci) [a] except *Haemophilus* species and *Neisseria gonorrhoeae:*

Zone Diameter (mm)	Interpretation

≥ 18	Susceptible (S)
14 to 17	Intermediate (I)
≤ 13	Resistant (R)

[a] These zone diameter standards for streptococci apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2[2].

For testing *Haemophilus* species:[b]

Zone Diameter (mm)	Interpretation
≥ 12	Susceptible (S)

[b] This zone diameter standard is applicable only to tests with *Haemophilus* species using *Haemophilus* Test Medium (HTM)[2].
The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.
No interpretive criteria have been established for testing *Neisseria gonorrhoeae.* This species is not usually tested.
Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for azithromycin.
As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15 mcg azithromycin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
Haemophilus influenzae ATCC 49247[a]	13 to 21
Staphylococcus aureus ATCC 25923	21 to 26
Streptococcus pneumoniae ATCC 49619[b]	19 to 25

[a] These quality control limits are applicable only to tests conducted with *H. influenzae* ATCC 49247 using *Haemophilus* Test Medium (HTM)[2].

[b] These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC 49619 using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2[2].

INDICATIONS AND USAGE

Azithromycin for Injection is indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the conditions listed below. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, please see **DOSAGE AND ADMINISTRATION** for dosing recommendations.

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus,* or *Streptococcus pneumoniae* in patients who require initial intravenous therapy.

Pelvic inflammatory disease due to *Chlamydia trachomatis, Neisseria gonorrhoeae,* or *Mycoplasma hominis* in patients who require initial intravenous therapy. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with Azithromycin for Injection.

Azithromycin for Injection should be followed by azithromycin by the oral route as required, (see **DOSAGE AND ADMINISTRATION**).

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative microorganism and its susceptibility to azithromycin. Therapy with azithromycin may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Azithromycin for Injection and other antibacterial drugs, Azithromycin for Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS
Azithromycin for Injection is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, or any macrolide antibiotic.

WARNINGS
Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported (see **CONTRAINDICATIONS**). Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure.** These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.
If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.
Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.
Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."
After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General
Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment; therefore, caution should be exercised when prescribing azithromycin in these patients.
Azithromycin for Injection should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes, (see **DOSAGE AND ADMINISTRATION**).
Local I.V. site reactions have been reported with the intravenous administration of azithromycin. The incidence and severity of these reactions were the same when 500 mg azithromycin were given over 1 hour (2 mg/mL as 250 mL infusion) or over 3 hours (1 mg/mL as 500 mL infusion), (see **ADVERSE REACTIONS**). All volunteers who received infusate concentrations above 2 mg/mL experienced local I.V. site reactions and, therefore, higher concentrations should be avoided.
Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization.
Prescribing Azithromycin for Injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients
Patients should be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin by the oral route simultaneously.
Patients should be directed to discontinue azithromycin and contact a physician if any signs of an allergic reaction occur.
Patients should be counseled that antibacterial drugs including Azithromycin for Injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Azithromycin for Injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Azithromycin for Injection or other antibacterial drugs in the future.

Drug Interactions
Aluminum- and magnesium-containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of orally administered azithromycin.
Administration of cimetidine (800 mg) two hours prior to orally administered azithromycin had no effect on azithromycin absorption.
Azithromycin given by the oral route did not affect the plasma levels or pharmacokinetics of theophylline administered as a single intravenous dose. The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses resulting in therapeutic steady-state levels of theophylline is not known. However, concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Therefore, until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.
Azithromycin given by the oral route did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.
The following drug interactions have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:
Digoxin - elevated digoxin levels.
Ergotamine or dihydroergotamine - acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.
Triazolam - Increased pharmacologic effect of triazolam by decreasing the clearance of triazolam.
Drugs metabolized by the cytochrome P^{450} system
- elevations of serum carbamazepine, terfenadine, cyclosporine, hexobarbital, and phenytoin levels.

Laboratory Test Interactions
There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found.

Pregnancy
Teratogenic Effects. Pregnancy Category B
Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose levels (i.e., 200 mg/kg/day by the oral route). These doses, based on a mg/m^2 basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg by the oral route. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of azithromycin for injection in children or adolescents under 16 years have not been established. In controlled clinical studies, azithromycin has been administered to pediatric patients (age 6 months to 16 years) by the oral route. For information regarding the use of azithromycin for oral suspension in the treatment of pediatric patients, refer to the **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections of the prescribing information for azithromycin for oral suspension 100 mg/5 mL and 200 mg/5 mL bottles.

Geriatric Use
Pharmacokinetic studies with intravenous azithromycin have not been performed in older volunteers. Pharmacokinetics of azithromycin following oral administration in older volunteers (65 to 85 years old) were similar to those in younger volunteers (18 to 40 years old) for the 5 day therapeutic regimen.
In multiple-dose clinical trials of intravenous azithromycin in the treatment of community-acquired pneumonia, 45% of patients (188/414) were at least 65 years of age and 22% of patients (91/414) were at least 75 years of age. No overall differences in safety were observed between these subjects and younger subjects in terms of adverse events, laboratory abnormalities, and discontinuations. Similar decreases in clinical response were noted in azithromycin- and comparator-treated patients with increasing age.

Azithromycin for Injection contains 114 mg (4.96 mEq) of sodium per vial. At the usual recommended doses, patients would receive 114 mg (4.96 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. The total sodium content from dietary and non-dietary sources may be clinically important with regard to such diseases as congestive heart failure.

ADVERSE REACTIONS

In clinical trials of intravenous azithromycin for community- acquired pneumonia, in which 2 to 5 I.V. doses were given, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. The majority of patients in these trials had one or more comorbid diseases and were receiving concomitant medications. Approximately 1.2% of the patients discontinued intravenous azithromycin therapy, and a total of 2.4% discontinued azithromycin therapy by either the intravenous or oral route because of clinical or laboratory side effects.

In clinical trials conducted in patients with pelvic inflammatory disease, in which 1 to 2 I.V. doses were given, 2% of women who received monotherapy with azithromycin and 4% who received azithromycin plus metronidazole discontinued therapy due to clinical side effects.

Clinical side effects leading to discontinuations from these studies were most commonly gastrointestinal (abdominal pain, nausea, vomiting, diarrhea), and rashes; laboratory side effects leading to discontinuation were increases in transaminase levels and/or alkaline phosphatase levels.

Clinical

Overall, the most common side effects associated with treatment in adult patients who received I.V./P.O. azithromycin in studies of community-acquired pneumonia were related to the gastrointestinal system with diarrhea/loose stools (4.3%), nausea (3.9%), abdominal pain (2.7%), and vomiting (1.4%) being the most frequently reported. Approximately 12% of patients experienced a side effect related to the intravenous infusion; most common were pain at the injection site (6.5%) and local inflammation (3.1%).

The most common side effects associated with treatment in adult women who received I.V./P.O. azithromycin in studies of pelvic inflammatory disease were related to the gastrointestinal system Diarrhea (8.5%) and nausea (6.6%) were most commonly reported, followed by vaginitis (2.8%), abdominal pain (1.9%), anorexia (1.9%), rash and pruritus (1.9%). When azithromycin was co-administered with metronidazole in these studies, a higher proportion of women experienced side effects of nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%), application site reaction, stomatitis, dizziness, or dyspnea (all at 1.9%).

No other side effects occurred in patients on the multiple dose I.V./P.O. regimen of azithromycin in these studies with a frequency greater than 1%.

Side effects that occurred with a frequency of 1% or less included the following:

Gastrointestinal: dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis

Nervous System: headache, somnolence

Allergic: bronchospasm

Special Senses: taste perversion

Post Marketing Experience

Adverse events reported with orally administered azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship could not be established include:

Allergic: arthralgia, edema, urticaria, angioedema

Cardiovascular: arrhythmias, including ventricular tachycardia, hypotension. There have been rare reports of QT prolongation and *torsades de pointes*

Gastrointestinal: anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis and rare reports of tongue discoloration

General: asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal)

Genitourinary: interstitial nephritis and acute renal failure, vaginitis

Hematopoietic: thrombocytopenia

Liver/Biliary: abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death

Nervous System: convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope

Psychiatric: aggressive reaction and anxiety

Skin/Appendages: pruritus, rarely serious skin reactions including erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis

Special Senses: hearing disturbances including hearing loss, deafness and/or tinnitus, rare reports of taste perversion

Laboratory Abnormalities

Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:

with an incidence of 4 to 6%, elevated ALT (SGPT), AST (SGOT), creatinine

with an incidence of 1 to 3%, elevated LDH, bilirubin

with an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 750 patients treated with azithromycin (I.V./P.O.), less than 2% of patients discontinued azithromycin therapy because of treatment-related liver enzyme abnormalities.

DOSAGE AND ADMINISTRATION
(See INDICATIONS AND USAGE and CLINICAL PHARMACOLOGY.)
The recommended dose of Azithromycin for Injection for the treatment of adult patients with community-acquired pneumonia due to the indicated organisms is: 500 mg as a single daily dose by the intravenous route for at least two days. Intravenous therapy should be followed by azithromycin by the oral route at a single, daily dose of 500 mg, administered as two 250 mg tablets to complete a 7 to 10 day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response.
The recommended dose of Azithromycin for Injection for the treatment of adult patients with pelvic inflammatory disease due to the indicated organisms is: 500 mg as a single daily dose by the intravenous route for one or two days. Intravenous therapy should be followed by azithromycin by the oral route at a single, daily dose of 250 mg to complete a 7 day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with Azithromycin for Injection.
The infusate concentration and rate of infusion for Azithromycin for Injection should be either 1 mg/mL over 3 hours or 2 mg/mL over 1 hour.
Preparation of the solution for intravenous administration is as follows:
Reconstitution
Prepare the initial solution of Azithromycin for Injection by adding 4.8 mL of Sterile Water For Injection to the 500 mg vial and shaking the vial until all of the drug is dissolved. Since Azithromycin for Injection is supplied under vacuum, it is recommended that a standard 5 mL (nonautomated) syringe be used to ensure that the exact amount of 4.8 mL of Sterile Water is dispensed. Each mL of reconstituted solution contains 100 mg azithromycin. Reconstituted solution is stable for 24 hours when stored below 30°C or 86°F. Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.
Dilute this solution further prior to administration as instructed below.
Dilution
To provide azithromycin over a concentration range of 1 to 2 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin solution into the appropriate amount of any of the diluents listed below:
Normal Saline (0.9% sodium chloride)
1/2 Normal Saline (0.45% sodium chloride)
5% Dextrose in Water
Lactated Ringer's Solution
5% Dextrose in 1/2 Normal Saline
(0.45% sodium chloride) with 20 mEq KCl
5% Dextrose in Lactated Ringer's Solution
5% Dextrose in 1/3 Normal Saline
(0.3% sodium chloride)
5% Dextrose in 1/2 Normal Saline
(0.45% sodium chloride)
Normosol®-M in 5% Dextrose
Normosol®-R in 5% Dextrose
Final Infusion Solution

Concentration (mg/mL)	Amount of Diluent (mL)
1 mg/mL	500 mL
2 mg/mL	250 mL

It is recommended that a 500 mg dose of Azithromycin for Injection, diluted as above, be infused over a period of not less than 60 minutes.
Azithromycin for Injection should not be given as a bolus or as an intramuscular injection.
Other intravenous substances, additives, or medications should not be added to Azithromycin for Injection or infused simultaneously through the same intravenous line.

Storage
Store the white to off-white lyophilized cake at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. When diluted according to the instructions (1 mg/mL to 2 mg/mL), Azithromycin for Injection is stable for 24 hours at or below room temperature (30°C or 86°F), or for 7 days if stored under refrigeration (5°C or 41°F).

HOW SUPPLIED
Azithromycin for Injection is supplied in lyophilized form under a vacuum in a 10 mL vial equivalent to 500 mg of azithromycin for intravenous administration. Each vial also contains sodium hydroxide and 413.6 mg citric acid.

Product No.	**NDC No.**	
309810	63323-398-10	Packaged in tens

Vial stoppers do not contain natural rubber latex.

CLINICAL STUDIES

Community-Acquired Pneumonia
In a controlled study of community-acquired pneumonia performed in the U.S., azithromycin (500 mg as a single daily dose by the intravenous route for 2 to 5 days, followed by 500 mg/day by the oral route to complete 7 to 10 days therapy) was compared to cefuroxime (2250 mg/day in three divided doses by the intravenous route for 2 to 5 days followed by 1000 mg/day in two divided doses by the oral route to complete 7 to 10 days therapy), with or without erythromycin. For the 291 patients who were evaluable for clinical efficacy, the clinical outcome rates, i.e., cure, improved, and success (cure + improved) among the 277 patients seen at 10 to 14 days post-therapy were as follows:

Clinical Outcome	Azithromycin	Comparator
Cure	46%	44%
Improved Success	32%	30%
(Cure + Improved)	78%	74%

In a separate, uncontrolled clinical and microbiological trial performed in the U.S., 94 patients with community-acquired pneumonia who received azithromycin in the same regimen were evaluable for clinical efficacy. The clinical outcome rates, i.e., cure, improved, and success (cure + improved) among the 84 patients seen at 10 to 14 days post-therapy were as follows:

Clinical Outcome	Azithromycin
Cure	60%
Improved	29%
Success (Cure + Improved)	89%

Microbiological determinations in both trials were made at the pre-treatment visit and, where applicable, were reassessed at later visits. Serological testing was done on baseline and final visit specimens. The following combined presumptive bacteriological eradication rates were obtained from the evaluable groups:
Combined Bacteriological Eradication Rates
for Azithromycin

(at last completed visit)	Azithromycin
S. pneumoniae	64/67 (96%)[a]
H. influenzae	41/43 (95%)

M. catarrhalis	9/10
S. aureus	9/10

[a] Nineteen of twenty-four patients (79%) with positive blood cultures for *S. pneumoniae* were cured (intent to treat analysis) with eradication of the pathogen.

The presumed bacteriological outcomes at 10 to 14 days post-therapy for patients treated with azithromycin with evidence (serology and/or culture) of atypical pathogens for both trials were as follows:

Evidence of Infection	Total	Cure	Improved	Cure + Improved
Mycoplasma pneumoniae	18	11 (61%)	5 (28%)	16 (89%)
Chlamydia pneumoniae	34	15 (44%)	13 (38%)	28 (82%)
Legionella pneumophila	16	5 (31%)	8 (50%)	13 (81%)

ANIMAL TOXICOLOGY

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs treated with azithromycin at doses which, expressed on a mg/kg basis, are only 2 times greater than the recommended adult human dose and in rats at doses comparable to the recommended adult human dose. This effect has been reversible after cessation of azithromycin treatment. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10 days to 30 days. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (30 mg/kg dose) at observed C_{max} value of 1.3 mcg/mL (6 times greater than the observed C_{max} of 0.216 mcg/mL at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed C_{max} value of 1.5 mcg/mL (7 times greater than the observed same C_{max} and drug dose in the studied pediatric population). On mg/m^2 basis, 30 mg/kg dose in the rat (135 mg/m2) and 10 mg/kg dose in the dog (79 mg/m2) are approximately 0.4 and 0.6 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. This effect, similar to that seen in the adult animals, is reversible after cessation of azithromycin treatment. The significance of these findings for animals and for humans is unknown.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.

APP Pharmaceuticals, LLC
Schaumburg, IL 60173

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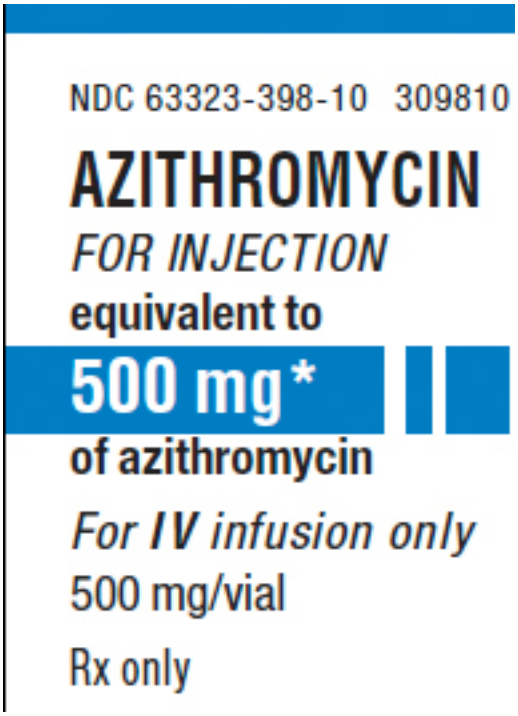
PACKAGE LABEL - PRINCIPAL DISPLAY - Azithromycin 500 mg Vial Label

NDC 63323-398-10
309810
AZITHROMYCIN FOR INJECTION
equivalent to
500 mg* of azithromycin
For IV infusion only
500 mg/vial
Rx only



PACKAGE LABEL - PRINCIPAL DISPLAY - Azithromycin 500 mg Vial Tray Label
NDC 63323-398-10
309810
AZITHROMYCIN FOR INJECTION
equivalent to
500 mg/vial of azithromycin
For IV infusion only
To yield 100 mg/mL* of solution when reconstituted as directed.
Rx only
10 vials

NDC 63323-398-10 309810

AZITHROMYCIN

FOR INJECTION

equivalent to

500 mg/vial

of azithromycin

*For **IV** infusion only*

To yield 100 mg/mL* of solution when reconstituted as directed.

Rx only

10 Vials